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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
23 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF COMPOUNDS FOR THE PREVENTION OF DRUG-INDUCED CELL TOXICITY

(57) Abstract: The present invention relates to the use of compounds for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity, such as nephrotoxicity and ototoxicity, in particular where the cell toxicity is induced by a medical treatment. In a preferred embodiment the compounds have at least two nitrogen atoms, more preferably at least two amino groups. The compounds according to the invention are capable of blocking binding of cell toxic compounds to the megalin receptor, and thereby inhibiting uptake of the cell toxic compounds into cells. The invention further relates to novel compounds for use in said treatment, as well as a method for reducing the cell toxicity of cell toxic compounds, more particularly gentamicin.

WO 2004/084876 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/132 A61K31/16 A61K31/198 A61K31/4196 A61K31/445
A61K31/495 A61K31/53 A61K31/7008 A61P39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 364 521 A (MERCK & CO INC) 21 August 1974 (1974-08-21) the whole document	1
P,X	WO 03/080103 A (MAX DELBRUECK CENTRUM ; WILLNOW THOMAS (DE)) 2 October 2003 (2003-10-02) abstract; claims 1,18,30,31 page 9, line 15 - page 10, line 5	1,3,19, 29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2004	18. 11. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/053519 A (BURNS MARK ROBERT ; BANDUIR NAND (US); ORIDIGM CORP (US); GRAMINSKI GE) 11 July 2002 (2002-07-11) abstract page 11, line 30 - page 21, line 5 page 36, lines 11-20 page 9, line 21 - page 10, line 6	1,2,4-6, 19-21, 28, 35-37, 47-49
X	WO 99/02145 A (DURANT GRAHAM J ; GWYNNE DAVID I (US); CAMBRIDGE NEUROSCIENCE INC (US)) 21 January 1999 (1999-01-21) the whole document	1-21,24, 28, 35-37, 47-49
X	EP 0 483 634 A (HOECHST ROUSSEL PHARMA) 6 May 1992 (1992-05-06) abstract page 3, line 12 - page 7, line 50; claims 1-14	1-5, 7-13, 15-21, 24,28, 35,47-49
X	DE 100 53 506 A (MAX DELBRUECK CENTRUM) 2 May 2002 (2002-05-02) the whole document	1,2, 4-11, 18-21, 28, 35-37, 47-49
X	WO 89/05637 A (US BIOSCIENCE) 29 June 1989 (1989-06-29) abstract; examples 1-4 page 2, paragraphs 1,3	1,4-6, 19,36, 37,47-49
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X	US 6 130 217 A (ARNOLD LEE DANIEL ET AL) 10 October 2000 (2000-10-10) column 1, line 50 - column 21, line 20 abstract	1,2,4, 7-13, 15-21, 28,35-37

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MILAM K M ET AL: "REDUCTION IN CIS DIAMMINEDICHLOROPLATINUM-II-INDUCED CYTOTOXICITY SISTER CHROMATID EXCHANGE AND DNA INTERSTRAND CROSS-LINKS IN 9L CELLS TREATED WITH THE POLYAMINE BIOSYNTHESIS INHIBITOR 2R 5R-6 HEPTYNE-2 5-DIAMINE" CANCER RESEARCH, vol. 49, no. 24 PART 1, 1989, pages 6945-6948, XP008033957 ISSN: 0008-5472 abstract page 6946, column 2 - page 6947, column 2, paragraph 3; figure 1; tables 1,2	1,4-6, 19-21, 28,29, 32,33, 35-37, 47-49
X	HEYS, STEVEN D. ET AL: "Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine: results of a randomized controlled trial" INTERNATIONAL JOURNAL OF ONCOLOGY , 12(1), 221-225 CODEN: IJONES; ISSN: 1019-6439, 1998, XP008033963 abstract	1,4-6, 17, 19-21, 28,35, 36,47-49
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X	FAN DOMINIC ET AL: "Reversal of multidrug resistance in murine fibrosarcoma cells by thioxanthene flupentixol" INVESTIGATIONAL NEW DRUGS, vol. 12, no. 3, 1994, pages 185-195, XP008033946 abstract	1,2,4,5, 15-17, 19-21, 28, 35-37, 47-49

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIN P K T ET AL: "The synthesis and in vitro cytotoxic studies of novel bis-naphthalimidopropyl polyamine derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 14, 17 July 2000 (2000-07-17), pages 1609-1612, XP004209715 ISSN: 0960-894X the whole document	1-37
A	EDWARDS M L ET AL: "POLYAMINE ANALOGUES WITH ANTITUMOR ACTIVITY. POLYAMINE ANALOGUES WITH ANTITUMOR ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 33, no. 5, 1 May 1990 (1990-05-01), pages 1369-1375, XP000604648 ISSN: 0022-2623 the whole document	1-37
X	WIEBKIN P ET AL: "INHIBITION OF METABOLISM MEDIATED CYTO TOXICITY BY 1 1 DI SUBSTITUTED HYDRAZINES IN MOUSE MASTO CYTOMA LINE P-815 CELLS" BIOCHEMICAL PHARMACOLOGY, vol. 31, no. 18, 1982, pages 2921-2928, XP001199476 ISSN: 0006-2952 the whole document	1
X	KONDRATOV R V ET AL: "Small molecules that dramatically alter multidrug resistance phenotype by modulating the substrate specificity of P-glycoprotein" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 98, no. 24, 20 November 2001 (2001-11-20), pages 14078-14083, XP002259950 ISSN: 0027-8424 the whole document	1-5, 7-13, 15-22, 28, 35-37, 47-49
X,P	WO 03/066572 A (OCHSNER CYNTHIA E ; COPP RICHARD R (US); FAHL KATHLEEN L (US); FAHL WI) 14 August 2003 (2003-08-14) the whole document	1,2,4-6, 19-21, 35-37, 47-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2004/000205

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-37, 47-49 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

remark: diaminomethane and piperidine are not compounds according to the structural definition of formula 1

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-37,47-49 (partially)

Use of a compound of formulae I-VI for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity.

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2. claims: 1-37,47-49 (partially) 38-41

Use of a moiety of gentamicin for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity.

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3. claims: 47-49 (partially) 42-46

A compound of formula VII and uses thereof.

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4. claims: 50-61

Method of reducing cell toxicity of a therapeutic agent comprising at least one cell toxic compound, said method comprising reducing the number of cationic groups from said at least one cell toxic compound.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000205

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Information on patent family members

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